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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,311	04/11/2006	Nicola Anne Burgess	13001015PCTUS	5452

23565 7590 03/07/2007

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EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,311	BURGESS, NICOLA ANNE	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-6 and 13-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *July 20, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment*.

DETAILED ACTION

1. Applicant's election with traverse of Group IV, claims 7-12, in the reply filed on January 8, 2007 is acknowledged. The traversal is on the ground(s) that the groups fail to define compositions and methods with properties so distinct as to warrant separate examination and search. This is not found persuasive because the compositions of Groups I, II, and VII may be a DNA, RNA or protein molecule while Group III is a polypeptide that may be an antibody, each of these molecules are structurally and functionally distinct. The methods of Groups IV-VI and VIII while involving screening, each include different steps and a different endpoint: treatment of ovarian cancer, interaction with CDCP1, modulating expression of CDCP1, and diagnosis of ovarian cancer. Thus, the groups are independent and distinct as set forth in the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

2. Claïms 1-6 and 13-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 8, 2007.

3. Claims 7-12 are under examination.

Information Disclosure Statement

4. The information disclosure statement filed July 20, 2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the document WO 02/04508 A1 is not in English and has not been considered. The remaining documents on the IDS have been considered by the examiner and an initialed copy of the IDS is included with this office action.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

5. The disclosure is objected to because of the following informalities: the specification contains typographical errors. For example, on page 16 line 1 "admixing" should read "mixing" and on page 30 line 28 "that is" should read 'that it is".

Appropriate correction is required throughout.

6. The use of the trademarks GeneGun®, Marathon™, Sypro™, Storm™, ZipTips™, and Sybr® have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The appropriate trademark symbols for Sypro™, Storm™, and Sybr® have not been included in this application. Appropriate correction is required for all trademarks throughout.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 8-9 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a.) Claim 8 is indefinite for reciting a "functionally-active fragment, derivative or analogue thereof". It is not clear what a functionally active fragment, derivative or analogue of the antibody is. What is the function? Binding, antibody dependent cytotoxicity, complement dependent cytotoxicity, etc.? How is the antibody derived? Label, altered sequence, etc.?

b.) Claim 12 is indefinite for reciting "activity of the CDCP1 polypeptide". It is not clear what is the activity of a CDCP1 polypeptide.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method for the treatment and/or prophylaxis of ovarian cancer comprising administering a therapeutically effective amount of an agent which interacts with or modulates the expression or activity of a CDCP1 polypeptide wherein the agent is an antibody, functionally-active fragment, derivative or analogue therof wherein the antibody is monoclonal, polyclonal, chimeric, humanized or bispecific, or is conjugated to a therapeutic moiety, detectable label, second antibody or

a fragment thereof, an effector or reporter molecule, a cytotoxic agent or cytokine. The claims are also broadly drawn to a method for the treatment and/or prophylaxis of ovarian cancer comprising administering a therapeutically effective amount of a composition comprising a CDCP1 polypeptide wherein the polypeptide comprises the amino acid sequence of SEQ ID No. 1 or is a derivative having one or more amino acid substitutions, modifications, deletions or insertions relative to the amino acid sequence of SEQ ID No. 1 which retains the activity of the CDCP1 polypeptide.

The specification discloses a polyclonal antibody that recognizes and binds to the CDCP1 polypeptide in ovarian cancer cells (page 35 example 4 and table top of page 36). The specification discloses internalization of the antibody/polypeptide complex 2 hours after binding (page 37). The specification does not disclose whether binding and/or internalization of the antibody/polypeptide complex leads to cell death.

Applicant has not provided any direction or guidance to assist one skilled in the art in the selection of all possible agents, peptide fragments, or antibody fragments, nor is there evidence provided that all such fragments would be therapeutically effective. Further, the as filed-specification fails to address the following issues:

1.) what amount of the antibody is considered to be therapeutically effective amount as a treatment or a prophylactic
2.) would administration of the CDCP1 antibody be effective for treatment of ovarian cancer
3.) would the CDCP1 polypeptide be therapeutically effective in treating or preventing ovarian cancer
4.) what derivative of the CDCP1 polypeptide, substitutions, modifications, deletions or insertions relative to the amino acid sequence of SEQ ID No. 1 would retain the activity of the CDCP1 polypeptide

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual tumorous disease. It is well known in the art that tumor cells in vivo simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes (Ezzell; page 48, column 2, paragraph 2). Forni, et al. (Cancer Research, 2000, 60; 2571-2575) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack (see page 2571, right column). Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a few patients with established tumors display objective and in any event temporary responses (see page 2571, right column). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy *in vivo*. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

Donnelly J. (Nature Medicine, 11(9): 1354-1356, Nov. 2003) states "treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future" (see page 1354 lines 13-17). Further, DeGruijl T. D. et al (Nature Medicine, 5(10): 1124-1125, Oct. 1999) state that a variety of anti-tumor vaccine trials have been undertaken and in spite of the large number of these trials, and the plethora of distinct approaches

investigated, there has been little evidence of clinical efficacy. DeGruijl also states "precise correlates of clinical effects and immunological responses have been lacking" (see page 1124, left column).

It has been art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to bedside) is a quantum leap (Chatterjee et al., Cancer Immunology and Immunotherapy, 38:75-82, 1994). Bodey B. et al (Anticancer Research, 20:2665-2676, 2000) acknowledge that general immune activation directed against the target antigens contained within cancer vaccines has been documented in most cases and tumor specific cytotoxic T lymphocytes (CTLs) can be isolated from the solid tumors, draining lymph nodes, metastatic effusions, and peripheral blood of cancer patients. However, attempts at active specific immunotherapy using cancer vaccines have met with little success in clinical trials (see abstract and page 2668). "Peptide vaccination against tumor antigens can induce powerful systemic CTL responses. However, in the majority of patients, no tumor regression is noted" (see page 2673, left column). Lee, et al. (Journal of Immunology 163: 6292-6300, 1999) also disclose that a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the peripheral mononuclear cells of cancer patients, though such a response does not associate with a clinically evident regression of metastatic melanoma. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated

that they no longer express cancer cell specific molecules (see Bodey page 2673, right column). "Use of cancer vaccines to stimulate the immune system may be in vain, if the particular tumor associated antigens represented in the vaccine preparation are no longer present on the most advanced subsets of cancer cells" (see Bodey pages 2673-2674).

Regarding fragments of the antibody, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proc Natl Acad Sci USA, 1982. Vol. 79, page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibody fragments as defined by

the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of a CDCP1 antibody in unspecified order have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Regarding the derivative of a CDCP1 polypeptide, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess, et al., Journal of Cell Biology, 1990. Vol. 111, pages 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar, et al. Molecular and Cellular Biology, 1988. Vol. 8 No. 3, pages 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (Schwartz. et al., Proc Natl Acad Sci USA, 1987. Vol. 84, pages 6408-6411). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase (Lin, et al. Biochemistry USA, 1975. Vol. 14 pages 1559-1563).

These references demonstrate that even a single amino acid substitution or what

appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. The results of the construction of synthetic proteins remain very unpredictable as Burgess, et al., Lazar, et al., Schwartz, et al., and Lin, et al. conclusively demonstrate.

There is insufficient evidence that would lead the skilled artisan to predict the ability to induce tumor immunity and to eliminate recurrent tumorous disease by treating and individual with an antibody to CDCP1, a CDCP1 polypeptide, or fragments thereof. The specification does not teach how to determine a functional fragment of the CDCP1 polypeptide nor what derivatives of the CDCP1 polypeptide would be therapeutically effective.

In view of the lack of predictability of the art to which the invention pertains and the lack of established clinical protocols for effective cancer therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for therapeutically and prophylactically treating ovarian cancer, commensurate in scope with the claimed invention.

Conclusion

11. No claims are allowed.

12. Claims 7-12 are free of the prior art. The closest prior art is Scherl-Mostageer, et al. (Oncogene, 2001. Vol. 20, pages 4402-4408, as cited on the IDS). Scherl-Mostageer, et al. teach detection of CDCP1 expression in colon cancer cells by RT-PCR (figure 5). Scherl-Mostageer, et al. teach expression of CDCP1 is significantly increased in colon cancer cells and moderately increased in lung and breast cancer cells. Scherl-Mostageer, et al. do not teach or reasonably suggest a method for the treatment or prophylaxis of ovarian cancer by administration of an agent which modulates the expression of a CDCP1 polypeptide.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow, Ph.D.

February 26, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

<!--StartFragment-->RESULT 3
US-09-899-569A-4
; Sequence 4, Application US/09899569A
; Patent No. US20020142003A1
; GENERAL INFORMATION:
; APPLICANT: No. US20020142003Albert Schweifer
; APPLICANT: Marwa Scherl-Mostageer
; APPLICANT: Wolfgang Sommergruber
; APPLICANT: Roger Abseher
; TITLE OF INVENTION: Tumorassoziiertes Antigen (B345)
; FILE REFERENCE: 0652.2280001
; CURRENT APPLICATION NUMBER: US/09/899,569A
; CURRENT FILING DATE: 2001-07-06
; PRIOR APPLICATION NUMBER: DE 100 33 080.0
; PRIOR FILING DATE: 2000-07-07
; PRIOR APPLICATION NUMBER: DE 101 19 294.0
; PRIOR FILING DATE: 2001-04-19
; PRIOR APPLICATION NUMBER: US 60/243,158
; PRIOR FILING DATE: 2000-10-25
; PRIOR APPLICATION NUMBER: US 60/297,747
; PRIOR FILING DATE: 2001-06-14
; NUMBER OF SEQ ID NOS: 40
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 4
; LENGTH: 836
; TYPE: PRT
; ORGANISM: Homo sapiens
US-09-899-569A-4

Query Match 99.8%; Score 4385; DB 3; Length 836;
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Matches 834; Conservative 2; Mismatches 0; Indels 0; Gaps 0;

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